11.

Pathology of *Dirofilaria* Infestation.[1]

Report of a case with chronic pulmonary arteritis.

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(Plates I-V).

The prominent increase in the recognition of *Dirofilaria immitis* infestation among dogs in the United States during recent years has made this a subject of some importance. Anatomic reports, although plentiful, have been generally incomplete and inconclusive. A case of extensive *Dirofilaria immitis* infestation in a gray wolf has recently come under our observation, the study of which forms the basis of this report. In view of the gaining importance of the disease it is of value to review briefly the literature on the subject and to discuss its various features.

The occurrence of this type of parasitism in the gray wolf, as far as we can determine, has not been reported in detail although there are frequent records of its appearance in dogs. Textbooks, however, refer to the occurrence of *Dirofilaria* in foxes, wolves, muskrats, raccoons, and occasionally other animals. Infestation with *Dirofilaria immitis* does not occur in man and conversely *Filaria bancrofti* is not observed in animals except perhaps in primates.

The presence of worms in the heart of the dog was first reported by Peysson in 1806 and by Von Gruby and Delafond in 1843. Leidy named the parasite *Filaria immitis*. Raillet and Henry in 1911 established the genus *Dirofilaria*, the most common species of which is *Dirofilaria immitis* (*dirus*, meaning cruel), a designation which has remained to the present. The members of the group besides *D. immitis* are: *D. magalhaes* and *D. repens*. The genus *Dirofilaria* is characterized by the absence of oral labia and by the possession of very inconspicuous cephalic papillae.

Shattock in 1881 observed worms in the cardiac chambers of a dog in Japan and found many parasites partly embedded in a post-mortem blood clot, which extended into the pulmonary artery and its larger branches.

In 1886, J. R. Figueira de Saboia described the presence of male and adult filaria in the chamber of the left ventricle of the heart of a child and referred them to De Magalhaes for study. A statement of the illness of the child was not given; the blood was not known to have been examined for larvae. The role of the parasite in the child's illness is therefore unknown. These were designated *D. magalhaes*. This occurrence in the child plus one case of *D. repens* found in man by Skrjbin, Althausen and Schulman (1930), represent the only recorded instances of infestation in man by a related species of *Dirofilaria*.

[1] From the laboratories of the Mt. Sinai Hospital and the New York Zoological Park.

Woods, in 1885, observed that *Dirofilaria* infestation was a common disease throughout the coastal cities of China. In one of his cases a continuous coil of filaria was found extending from the right hepatic vein, through to the inferior vena cava, into the right auricle, through the tricuspid valve orifice into the chamber of the right ventricle. The left auricular chamber was packed with the nematodes connected with a mass fourteen inches long extending into both lungs through the pulmonary arteries. He was of the opinion that the ova were introduced into the animal by drinking from stagnant pools. F. Fullerborn and others, however, definitely established the fact that the disease is transmitted by means of the mosquito which functions as the intermediate host.

De Magalhaes (1892) emphasized the difference between *Dirofilaria immitis* and *Filaria bancrofti.* This investigator felt that whereas *Dirofilaria immitis* was generally found in the chamber of the right heart and in its great vessels, *Filaria bancrofti* was constantly encountered within the lymphatics. The recent studies of Augustine and his co-workers demonstrated, on the other hand, that the microfilaria of *D. immitis* could occasionally also be found within the lymphatic channels.

The first comprehensive articles on *Dirofilaria immitis* appeared in 1889 with the reports by Janson of post-mortem findings in 41 dogs. The parasites were most frequently found in the right cardiac chambers and its great vessels but only rarely within the cavity of the left ventricle, aorta or femoral artery. Pulmonary emboli were found in the branches of the pulmonary artery with infarction, necrosis and even abscess formation of the pulmonary parenchyma. The adult parasites were found in the inferior vena cava, extending into the hepatic vein, producing thereby congestion of the liver with secondary congestion of the portal vein and subsequent ascites. In one heart a worm was seen passing through a patent foramen ovale with one half of its body located in each auricle. This offers a ready explanation, at least in some instances, of a mechanism for the entrance of the parasite into the general systemic circulation. Janson further described 26 cases of hypertrophy of the right ventricle and in some specimens marked dilatation, 5 of obstruction of the pulmonary artery, 2 examples of aneurism of the pulmonary artery without thrombosis, 9 of aneurism of the pulmonary artery with thrombosis, 13 of "interstitial hepatitis," 19 instances of hydrothorax and ascites, 1 of edema of the subcutaneous tissues, 5 examples of worms entangled in the chordae tendinae. He referred to the presence of chronic endocarditis which he felt had proceeded the filariasis, and was aggravated by the presence of the nematodes. In the lungs of acute cases he found "anemia and atelectasis with and without edema." A "nut-meg liver" was not infrequently observed. The kidney exhibited "parenchymatous, catarrhal and interstitial changes." On the basis of these anatomical findings Janson believed that the embryos of *Dirofilaria immitis* escaped from the body mostly in the urine. This concept has been subsequently shown to be erroneous, for although microfilaria are known to pass through the kidneys, the renal lesions, described by Janson, correspond to the so-called spontaneous interstitial nephritis, so commonly observed in animals (Horn, 1937). However the possibility of any exaggeration of this process by the toxins elaborated by the parasite cannot be negated.

Van Meter (1892) reported the gross finding of a case which included chronic endocarditis of the tricuspid valve, attributed to the presence of the parasite. The inter-auricular septum was perforated (foramen ovale?) and the nematodes were also found in the pulmonary vein. French (1899) reported the gross findings of a case in a bitch whose litter of pups three months previously died with diarrhea. He found some small worms in the intestines of the offsprings and raised the question of the possibility of the placental transmission of the disease. Riesman (1903) described an animal with dyspnea, who fell to the ground while trotting and on examina-

tion revealed markedly accentuated heart sounds, a murmur (type not described), cyanosis and ascites. Necropsy disclosed a "white thrombus" in the right heart enmeshing a parasite and slightly hypertrophied right cardiac chambers. The left branch of the pulmonary artery was completely occluded with an ante-mortem thrombus. Larvae were not demonstrated. He stated that 50% of the canine population of China and Japan harbored the worm and that the embryos were found more easily during the night than the day. The attention of Hopkins three years afterwards was drawn to this disease when three of his dogs being used for experimental purposes died under anesthesia. These and three additional animals showed gross findings typical of *immitis* infestation. In one case, the wall of the pulmonary artery two centimeters above the valve was studded with fine granules which on section proved to be subendothelial fibrous nodules.

In 1919 Lynch anesthetized an infected dog in whose blood he had demonstrated many larvae and proceeded to observe the vessels of the omentum drawn over the stage of a microscope. He observed the microfilaria moving about in the capillaries but found no evidence of plugging of the vessels. In the same year Ryan reported the case of a dog which had contracted the disease in the northern temperate zone of the United States. Kowakami, in 1919, studied the distribution of the microfilaria in the body and found them to be most commonly within the lungs, heart and respiratory muscles. Yano (1927) gave the order of frequency of the involved organs as heart, lung, kidney and asserted that 20% of the dogs about Tokio were infected. Histological studies of the kidneys of his animals disclosed the typical lesion found in the so-called interstitial nephritis of dogs. In one instance, however, the author found multiple hemorrhages and in another, multiple zones of infarction. Microfilaria were found in scattered capillaries of the cortex. In advanced cases there was renal atrophy. It was Yano's opinion that the microfilaria did not form glomerular emboli but suggested that the renal changes might be of toxic origin. A few of the vitally stained microfilaria injected into healthy dogs were recovered in the urine and were at times associated with renal hemorrhage. Blood eosinophilia was not observed. His attitude concerning the toxic origin of renal changes was strengthened by the fact that when a centrifuged extract of female *Dirofilaria immitis* was injected into mice, distinct changes, resembling those found in dogs, were elicited in the kidneys.

Yamanouchi (1928) attempted to study the distribution of experimentally introduced larvae in the kidneys of mice. When he injected living larvae into mice both intravenously and into the renal artery, he found the embryos in the capillaries of the cortex located, for the most part, in the capillaries of the glomeruli. Heat-killed larvae were distributed mostly in the afferent vessels of the glomeruli but none in the excretory tubular system, the kidney, ureters or bladder. Blackberg and Ashman (1930) emphasized the pronounced effect of filarial infestation upon cardiac function. Electrocardiographic tracings taken on dogs during exercise disclosed an inversion of the T wave in lead I and almost complete disappearance of the T wave in lead II. In view of the similiarity of the tracings to those seen during attacks of angina pectoris in man the changes were attributed to an inadequate blood supply resulting in a deficient oxygen supply to the cardiac muscle.

Hayes (1933) reported that 80% of the dogs in Florida that he examined had *Dirofilaria immitis* infestation. Hayes asserted that in 1931-1933 this disease caused more loss than canine distemper. He referred to the increase of the disorder in recent years throughout the southern tiers of the United States. It was panzootic in 1932, throughout Georgia, Florida, Alabama, Mississippi and Louisiana. The most common symptoms were poor general condition, a rough coat, lack of endurance, a lazy attitude developing into extreme weakness, progressive anemia, often chronic in-

digestion, accompanied by ascites and generalized dropsical swellings. Mild infestations produced less marked symptomotology and with good care the animals could go on indefinitely without any apparent discomfort.

In recent years Augustine and his co-workers studied the question of the filtration of microfilaria by lymph nodes. They found that the larvae were not phagocytosed, as were the erythrocytes, and that they could pass through the lymph nodes with slight hindrance. In another experiment, after exsanguinating a normal dog and substituting the blood of a heavily infested dog, they were able to collect living embryos in the lymphatic channels and in the spinal fluid. Thus, they demonstrated that the larvae may escape from the blood vessels, traverse tissues and enter the lymphatic system. The histological findings were the same in both donor and recipient. Microfilaria were disseminated in every part of the body. Great numbers were present in the lungs, liver and kidney. None was found in the stomach or intestines. In the lungs many were discovered in the large arteries, veins, capillaries and occasionally in the alveoli. Many lay in the veins and sinusoids of the liver. The kidneys manifested the microfilaria most frequently in the glomeruli, some edema was present but no pathological changes. They usually followed the course of the capillaries. Very few were recovered in 40 cc. of urine of a heavily infected dog. Evidence that they passed through the glomeruli to the efferent vessels was offered by the presence of the organisms in the renal veins. Few existed in the capsule of the spleen but many were in the pulp. The lymph nodes likewise showed few and those were mostly in the intermediary sinuses in the depths of the node. Great numbers were embedded in the myocardium, particularly the left ventricle. They were mostly in the capillaries but in some instances lay outside the capillaries parallel to the fibers. A tremendous number rested in the bood vessels of the pericardium. No cellular reaction to the microfilaria was evident anywhere.

To settle the question of the behavior of the larvae in the capillaries and the reason for the absence of embolic phenomena these workers injected the microfilaria into bats and observed their behavior in the capillaries of the bat's wing. This was a superior method to that of Lynch, who examined the exposed mesentery of a dog, because it did not disturb the normal physiological conditions of the host. "The anterior end of the microfilaria were constantly active in searching movements. As the blood vessels branch and become smaller the organisms may eventually enter capillaries which are obviously somewhat contracted and proceed into them until the lumen gets too small, when they never were observed to escape or make permanent plugs. They simply backed out. That is the reason why microfilaria do not form emboli. Whenever these active organisms became stuck in a capillary they merely moved backwards against the current until they were safely on their way elsewhere."

Joyeux and Cabassu (1935) found microfilaria in the blood of 19 out of 26 dogs examined in the area known as Camargue. They identified the adult *Dirofilaria* in one of two foxes they studied. Yamamoto (1936) described microfilaria in the uterus and detected their escape in the menstrual flow. However, he did not regard this fact as definite proof of passage through the placenta. Ohashi, in the same year, established the fact that the larvae could be found in the skin of the eyelids, bulbar conjunctivae and membrana nictitans. A few embryos were present in the lacrimal secretion. He occasionally found that they worked their way into the vitreous body or produced hemorrhage about the optic nerve.

Hinman and Baker (1936) made a helminthic survey of 1,305 dogs from New Orleans and found 321, or 24.4%, infected with *Dirofilaria immitis*. They recovered the embryos in immature dogs and concluded that they may pass through the placenta. Diagnostic serological and intradermal tests in filaria were introduced independently by Taliaferro and

Hoffman, and also by N. H. Fariley (cited by Manson-Bahr 1935). The antigen was obtained from *Dirofilaria immitis.*

Nematodes have been found in the hearts of the harbor seal. According to Ross Nigrelli of the New York Aquarium this species belongs to the genus *Halocercus,* the members of which are common parasites of the lungs of other species of seals, dolphins and porpoises. This parasite not infrequently is mistaken for *Dirofilaria immitis.*

Report of a Case.

On December 12, 1937, a male wolf (*Canis nubilis*) died in the New York Zoological Park. He was observed to have had a distended abdomen during the previous four years.

Post-mortem Examination: The body was well developed and in fairly good condition. The dentition was good. The abdomen was moderately distended. The wall of the right heart was strikingly hypertrophied and the chambers tremendously dilated so that it appeared to be about twice the size of the left ventricle (Plate I, Fig. 1). The pulmonary ring was dilated and measured 6.5 cm. in circumference whereas the aortic ring measured 5.5 cm. A thrombus filled the right ventricle in which many adult round worms were enmeshed. These were identified by Lucker and McIntosh in E. W. Price's laboratory of the Bureau of Animal Industry, Washington, D. C., as *Dirofilaria immitis.* A reddish-brown, rough, irregular, endocardial nodule, 3 mm. in diameter, was found in the outflow tract of the right ventricle. A thrombus, with entrapped *Dirofilaria,* extended into the lumen of the pulmonary artery and of many of its branches. Many of the branches of the right pulmonary artery and some of the left showed aneurysmal dilatations and some were thrombosed. In the branches the thrombi were, for the most part, firmly adherent. Some were reddish-brown and others grayish-white, fibrotic and evidently organized (Plate I, Fig. 2). Some of the nematodes were still motile. The intima of the main stem of the pulmonary artery was roughened, due to shallow, fine, pit-like, closely grouped depressions. Along the intimal surfaces of the branches of the pulmonary arteries there was longitudinal and transverse bridging. Tranversing the lumina of some branches, in secant-like fashion was a network of slender, fibrous bands, strings and thin membranes, originating in the intima at one point and inserting at another (Plate I, Fig. 2), (Safir, 1932). The lungs weighed 1,370 grams together and presented many infarcted areas with associated areas of pneumonitis (Plate II, Fig. 1). The pulmonary veins exhibited no pathological changes. The larger radicles of the tracheo-bronchial tree were clear throughout. The hilar lymph nodes were large and succulent.

The peritoneal cavity was filled with 2,000 cc. of clear amber fluid. The liver was enlarged, weighed 1,900 grams and displayed evidence of marked acute and chronic passive congestion. Some areas manifested pseudo-adenomatous formation. There was one large cyst 4 cm. in diameter in the right lobe. A large thrombus containing *Dirofilaria* filled the right main branch of the hepatic vein and its smaller branches (Plate II, Fig. 2). The gall bladder and biliary system were normal. The spleen did not appear enlarged. A firm hemangioma, about 1 cm. in diameter, arose from the midportion. The gastro-intestinal tract showed evidence of severe passive congestion. Multiple minute mucosal hemorrhages were present. In addition many small, yellow, hard nodules 2 mm. in diameter were disseminated over the serosa of the small intestine. The kidneys were markedly congested. The spinal fluid was cloudy and on smear disclosed many gram positive cocci. The meninges had a dull fibrinous appearance. Pure cultures of staphylococcus were grown from the heart's blood and the spinal fluid. The or-

ganisms produced yellowish to light orange pigment but could not be definitely classified by fermentation tests.

Microscopic Findings: The myocardium revealed only degenerative changes. The intima of the main stem of the pulmonary artery was markedly thickened and showed pit formation. The adventitia was thickened and showed numerous perivascular infiltrations consisting chiefly of lymphocytes but also plasma cells and polymorphonuclear cells. The pericardium in this region revealed a membrane composed of fibrin with entrapped necrotic cells lying on the surface. The elastica Van Giesen stain disclosed marked reduplication and fragmentation of the elastic fibres. The elastic lamellae were of irregular thickness and often their continuity was interrupted.

The walls of the intra-pulmonic branches of the pulmonary artery were thickened and exhibited frequently a striking destruction with replacement of the elastic and muscle fibres of the media by connective tissue. The elastica was markedly fragmented (Plate III, Fig. 1). There was excessive thickening of the adventitia. The intima manifested a conspicuous focal thickening. In one place there was necrosis of the wall with inflammatory cell infiltration (Plate IV). The lumina of these vessels displayed thrombi in all stages of organization. The adjacent alveolar septa were very strikingly thickened and infiltrated with inflammatory cells. This interstitial reaction extended into the finer ramifications. The lung tissue in the immediate vicinity of the larger branches of the pulmonary artery showed collapsed alveoli, frequently containing polymorphonuclear cells and macrophages. Many of the smaller branches of the pulmonary artery were surrounded by a mantle of inflammatory cells and display a marked thickening of the wall and narrowing of the lumen (Plate III, Fig. 2). Some vessels disclosed entire replacement with fibrous tissue. There was also evidence of purulent bronchitis, obliterating bronchiolitis, pneumonia and edema. Organizing pneumonia was in evidence. One wide patch of lung tissue was completely fibrotic, suggesting a completely organized infarct. The ghost-like remains of its vessel of supply was present in its center (Plate III, Fig. 1). The lumen of this artery was completely filled with scar tissue indicating an organization of the original thrombus. A gram stain showed a small number of gram positive cocci in the lung tissue while an iron stain revealed large amounts of iron pigment in the walls of the larger arteries and in the macrophages (heart failure cells) which occupied the alveolar spaces. In the lumen of one bronchus an adult *Dirofilaria* was seen (Plate V, Figs. 1 and 2). The hilar lymph nodes revealed evidence of hyperplasia. A gram stain disclosed only an occasional gram positive coccus.

The capsule of the liver was slightly thickened. The hepatic architecture was severely distorted. There was marked central congestion and marked secondary atrophy of liver cells. In some places entire patches were devoid of liver cells and were replaced by cavernous sinusoids. Disse's spaces were widened and filled with granular material. The Kupfer cells were markedly swollen and some showed erythrophagocytosis. The biliary ducts were not increased. A large branch of the hepatic vein contained an organizing thrombus. An adult worm lay within the lumen next to the thrombus. An iron stain disclosed very little iron and the gram stain only occasional gram positive cocci.

The spleen was markedly congested. The pancreas displayed vascular congestion. The adrenals presented slight hemorrhage in the zone reticularis. The kidneys were the seat of marked congestion, edema and degeneration of the tubular epithelium. There was slight interstitial focal infiltrations of plasma cells.

Unfortunately the brain and spinal cord were lost and could not be examined microscopically. No larvae were detected in any of the tissues. All tissues were fixed in formalin.

The final diagnosis was: *Dirofilaria immitis* infestation of the right heart with thrombosis in the right heart, pulmonary artery and its branches, and the right branch of the hepatic vein; chronic arteritis of the pulmonary artery and its branches with aneurism formation of many of the branches and pulmonary arteriosclerosis; marked hypertrophy of the right ventricle and auricle with tremendous dilatation; chronic endocarditis of the outflow tract of the right ventricle; multiple pulmonary infarcts; chronic purulent bronchiolitis; chronic pneumonitis of all lobes; staphylococcus sepsis; severe acute and chronic passive congestion of the liver with atrophy and pseudoadenomatous formation; acute purulent meningitis; large cyst of the liver; and slight interstitial nephritis.

Comment.

A review of the reported cases, including the instance herein described, indicates that the usual cause of death in dirofilariasis of the pulmonary arterial tree is congestive right heart failure. Anatomically, it was evidenced in this case by right cardiac hypertrophy and excessive dilatation, an extreme degree of chronic passive congestion of the liver and ascites. From the character of the arterial lesions observed there is indication that one of the earliest effects on the pulmonary arteries may be a toxic degeneration of the pulmonary arterial wall caused by the humoral products of the adult parasites. This arteritis in turn may have caused the thrombosis in the pulmonary vessels, followed by the development of marked chronic changes in the vessel walls and organization of the thrombi. The hypertension of the pulmonary circuit thus engendered by the presence of such an occluding mechanism, caused dilation of the right ventricle and subsequent hypertrophy. The pulmonary hypertension may in turn be a contributing factor in the causation of the thickening of the intima and the endocardium. The endocarditis may well be a change de novo or possibly an exaggeration of a preceeding endocarditis which is so commonly found in animals of the older age group. Thrombus formation may also be provoked by this endocardial lesion. As the right heart fails, the slowing of the circulation produced in the great veins leading to the right heart, plus the presence of the adult parasites, would tend to foster further thrombosis in these places. We have then, four factors that may have a causative relationship to thrombus formation, namely: toxic arteritis, chronic endocarditis, slowing of the venous circulation, and the adult *Dirofilariae* acting as foreign bodies. The pulmonary arteriosclerosis in the case herein reported may be considered as secondary to the pulmonary hypertension.

The presence of this obstructing mechanism, together with the associated infarcts, whatever the pathogenesis of the latter may be, causes generalized anoxemia, as a result of the interference with the pulmonary circulation. This readily accounts for part of the symptom-complex that the diseased animals present, such as, dyspnea, cyanosis and weakness.

It is interesting in connection with the arterial lesions encountered to briefly mention the report of Clark and Graef of a case of Schistosomiasis mansoni in a twenty-one year old Puerto Rican girl who died of congestive failure. Post-mortem examination revealed a markedly dilated right heart. Evidence of arteritis and dilatation of the branches of the pulmonary artery with associated severe arteriosclerosis was noted. The authors were able to demonstrate the ova in the media and concluded that the arteritis was a specific response to the parasite, while the arteriosclerotic thickening was assumed to be secondary to the increased tension within the pulmonary arterial tree. We do not feel that the arteritis observed by us was caused by the presence of adult or embryonic parasites in the wall of the vessels. We could not demonstrate such a lesion as did Clark and Graef. On the

contrary, we are inclined to the view that the toxins elaborated by the adult *Dirofilaria* and their larvae may have caused the arteritis. The work of Yano, referred to above, in which he produced renal changes after injection of a centrifuged extract of female *Dirofilaria,* gives some support to this concept.

In the case reported here, the additional factor of severe infection must be held accountable as the immediate cause of the animal's death.

We failed to detect any microfilaria in the tissues we examined. This is not surprising when one considers the life cycle of the *Dirofilaria.* For it is known that the larvae produced by the adult filaria are not capable of maturing in the host and tend to disappear. They must pass through an intermediate host (mosquito) and be innoculated into a dog or other susceptible animal before they are capable of reaching an adult, sexually mature state. In our case, where the adult nematodes were apparently dying as they were entrapped in thrombi, fewer and fewer embryos were produced and thus none was seen in the tissues. The blood of the wolf was not examined before death.

It is apparent from what has been said that in infested animals with cardiac embarrassment, the additional toxic effect of an anesthetic on the cardiac muscle readily explains the cases of death ensuing during anesthesia reported in the literature.

Summary.

1. A review of the literature on the morbid anatomy of *Dirofilaria immitis* infestation in mammals is presented.

2. An instance of such infestation in a gray wolf dying of congestive heart failure and superimposed sepsis is described.

3. An unusual feature of arteritis with associated aneurysmal dilatation of the branches of the pulmonary artery is reported.

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EXPLANATION OF THE PLATES.

Plate I.

Fig. 1. Markedly dilated and hypertrophied right cardiac chamber.

Fig. 2. Right lung with pulmonary arteries opened to show old and fresh thrombi (A) and adult *Dirofilaria* (B). Note organizing network over intima (C).

Plate II.

Fig. 1. Right lower lobe (larger) and right upper lobe (smaller) showing areas of infarction and pneumonitis. Note aneurysmal dilation of pulmonary artery (A).

Fig. 2. Liver with hepatic vein containing thrombus and adult *Dirofilaria.*

Plate III.

Fig. 1. Cross section of a branch of the pulmonary artery showing complete organization of a thrombus. Elastica exhibits marked fragmentation and destruction. (Section taken from an infarcted area. Elastica-carmine stain).

Fig. 2. Smaller branch of pulmonary artery showing markedly thickened intima and narrowed lumen. (Elastica-carmine stain).

Plate IV.

Fig. 1. Wall of large branch of pulmonary artery showing purulent inflammation of intima (A) and thrombus in lumen (B).

Plate V.

Fig. 1. Low power view of lung showing longitudinal section of an adult *Dirofilaria* (A) lying within the bronchus, thickened wall of main branch of pulmonary artery revealing fibrosis (B) and a thrombus in lumen (C).

Fig. 2. Enlarged photograph of right lower corner of Fig. 1 showing portion of *Dirofilaria* lying within bronchus, and purulent bronchitis.